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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/580,037	POULIQUEN ET AL.	
	Examiner	Art Unit	
	ILEANA POPA	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 February 2011*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,5,7-19 and 22-30* is/are pending in the application.

4a) Of the above claim(s) *24-27,30-34,38 and 39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,5,7-19,22,23,28,29 and 35-37* is/are rejected.

7)☒ Claim(s) *28* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 2, 3, 6, 20, and 21 have been cancelled. Claims 24-27, 30-34, 38, and 39 have been withdrawn.

Claims 1, 4, 5, 7-19, 22, 23, 28, 29, and 35-37 are under examination.

2. All rejections pertaining to claims 3, 6, and 21 are moot because the applicant cancelled the claims in the reply filed on 02/10/2011.

The objections to claims 7 and 28 are withdrawn in response to the amendments filed on 02/10/2011.

Claim Objections

3. Claim 28 is objected to because of the following informalities: the recitation of "and in that it is obtained from the formulation of claim 1" is redundant as the claim already recite that the microparticles are obtained from the "non-covalent PO/interferon associations as defined in claim 1" (i.e., the formulation of claim 1). Appropriate correction is required.

Response to Arguments

Double Patenting

4. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees.

A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

5. Claims 1, 4, 5, 7-19, 22, 23, 28, 29, and 35 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3, 5, 7-10, 12-20, 22, 25, 26, 28, 29, 35 and 36 of copending Application No. 10/580,035. Although the conflicting claims are not identical, they are not patentably distinct from each other because both claim sets are drawn to the same polymer formulation for prolonged delivery of therapeutic agents. Although the instant claims recite interferon and not interleukin, one of skill in the art would have found it obvious to replace the interleukin with interferon. Thus, the instant claims and the application claims are obvious variants.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The applicant has requested that the obvious-type double patenting rejection set forth by the examiner be held in abeyance. The applicants' comments are acknowledged, however the rejection will be maintained until a terminal disclaimer is filed or claims are amended to obviate the rejection.

6. Claims 1, 4, 5, 7-19, 22, 23, 28, 29, and 35 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-20, 25 and 27 of copending Application No. 11/878,947, over claims 1-16, 21, 22, 24-26, 28 and 29 of copending Application No. 10/580,023, over claims 1-3, 5-16, 19, 21, 22, 24, 25, 28, and 29 of the copending Application No. 11/808,456, and over claims 1, 6-10, 15, 16, 18-21, 26-30, 38 and 39 of the copending Application No. 12/003,095. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims and the applications claims are drawn to the same polymer formulation for prolonged delivery of therapeutic agents. Thus, the instant claims and the application claims are obvious variants.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The applicant has requested that the obvious-type double patenting rejection set forth by the examiner be held in abeyance. The applicants' comments are acknowledged, however the rejection will be maintained until a terminal disclaimer is filed or claims are amended to obviate the rejection.

7. Claims 1, 4, 5, 7-19, 22, 23, 28, 29, and 35 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-10, 16, 18-24 of the U.S. Patent 7,683,024. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims and the patent claims are drawn to the same polymer formulation for prolonged delivery of therapeutic agents. Thus, the instant claims and the patent claims are obvious variants.

8. Claims 1, 4, 5, 7-19, 22, 23, 28, 29, and 35 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-21, 28-32 and 40 of U.S. Patent No. 6,630,171, in view of each Regalado et al. (Macromolecules, 1999, 32: 8580-8588, of record), Dupuis et al. (U.S. Patent No. 6,607,714), and Bromberg et al. (U.S. Patent No. 5,939,485). Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims and the patent claims are drawn to the same polymer formulation for prolonged delivery of interferon. The patent claims do not recite gel-forming properties. However, modifying the patent claims to obtain injectable solutions capable of *in situ* gelling is suggested by the prior art. Controlled and prolonged drug release via injectable formulations capable of gelling *in vivo* was routine in the prior art. The prior art also suggests that the polymer of the '171 patent is capable of forming a gel *in vivo* in the presence of physiological proteins. For example, the prior art teaches that incorporation of HG into hydrophilic polymers results in amphiphilic polymers which are

capable of sol to gel transition depending on the amphiphilic polymer concentration (see Regalado et al., p. 8580, column 1; p. 8587, column 2). Dupuis et al. teach that amphiphilic polymer solutions are capable of forming gels in the presence of serum proteins such as albumin (Examples 4 and 5). Bromberg et al. teach the necessity of using responsive polymers capable of forming a gel in the presence of an environmental stimulus (such as a stimulus present *in vivo*), wherein adjusting the concentration of the responsive polymer gives the desired sol to gel transition (Abstract; column 2, lines 17, 18, and 63-65 ; column 6, lines 43-56; column 11, lines 20-40, claims 5, 18, and 32). Based on these teachings as a whole, one of skill in would have known that the amphiphilic polymer of the '171 patent is capable of sol to gel transition. One of skill in the art would also have reasonably expected that the polymer at concentrations promoting the sol to gel transition would be able to form a gel when injected *in vivo*, because albumin is present in blood and in the interstitial fluid. Therefore, one of skill in the art would have been motivated to vary the polymer concentration such as to determine the proper concentration needed to obtain a liquid formulation capable to form a gel in the presence of albumin (claim 3). It is noted that by doing such, one of skill in the art would have obtained a formulation capable of forming a gel deposit *in vivo* in the presence of physiological proteins.

Thus, the instant claims and the patent claims are obvious variants.

The applicant argues that claim 1 is now directed to a specific polyamino acid formulation for the prolonged delivery of interferon. The cited references, namely US

Patent No. 6,630,171 in view of Regalado, Dupuis and Bromberg do not disclose every element of the claimed invention, and, therefore, the claimed invention is patentably distinct from the cited references.

This is not found persuasive. The polymer recited in the patent claims is the same as the instant polymer and thus, it must be capable of forming a gel when injected *in vivo*. Apart from arguments, the applicant did not provide any evidence to the contrary. Regalado, Dupuis and Bromberg were only cited as providing the evidence for this property.

The applicant argues that the current invention is not directed to gelling of amphiphilic polymer, but to the existence of a relation between the concentration C1 of the polyamino acid and an increase in the release time of interferon(s).

This is not found persuasive as the relationship between polymer concentration and gelling (i.e., increased release time) was recognized by the prior art (see the teachings of Bromberg et al. above). For this reason, the arguments regarding Regalado are not found persuasive; the rejection is based on a combination of references and not on Regalado alone.

The arguments related to Dupuis are immaterial to the instant rejection, which is not based on a composition comprising BSA. Dupuis was cited as providing evidence that the polymer recited in the patent claims is capable of forming a gel when injected *in vivo* (i.e., when coming in contact with the albumin present in blood).

The applicant argues that, as opposed to Bromberg et al. who teach the necessity of using responsive polymers capable of forming a gel in the presence of an environmental stimulus, the current invention was designed to obtain a liquid pharmaceutical formulation comprising an aqueous colloidal suspension of polyamino acid that can delay the release of the interferon, without using stimuli such as temperature or pH change. Bromberg does not teach any relation between a concentration of polymer and the increase in the release time of interferon *in vivo*.

This is not found persuasive, as the patented and the instant polymers are the same and thus, they must necessarily have the same properties. The combination of Regalado, Dupuis and Bromberg provides evidence to this effect. Bromberg was only cited for the teaching that the relation between polymer concentration and gelling in the presence of environmental stimuli was known in the prior art. Dupuis provides evidence that the patented polymer is capable of forming a gel in the presence of albumin. One of skill in the art would have known to adjust the concentration of the patented polymer to achieve the desired sol to gel transition when injected *in vivo* (i.e., in the presence of blood albumin or an environmental stimulus). Apart from arguments, the applicant did not provide any evidence to the contrary.

9. Claims 1, 4, 5, 7-19, 22, 23, 28, 29, and 35 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-10 and 12-22 of copending Application No. 11/658,803 because the instant claims and the application claims are drawn to the same polymer formulation for

prolonged delivery of interferon, wherein the polymer is capable of forming a gel (i.e., a depot) upon administration *in vivo* (i.e., in the presence of albumin). Since the polymer solution recited in the application claims is liquid before administration and forms a gel upon administration, it must have the polymer concentration and the viscosity recited in the instant claims. Thus, the instant claims and the application claims are obvious variants.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The applicant argues that the gel disclosed in copending Application No. 11/658,803 does not form upon administration *in vivo* but instead is the final form of the formulation before administration to the patient.

This is not found persuasive because none of the application claims is restricted to a gel formed before the *in vivo* administration. In fact, the application claims 19-22 recite that the composition can be formulated as a solution or a colloidal suspension, which forms a gel at the injection site (i.e., after administration *in vivo*).

The applicant argues that the application claims do not teach how to determine the critical concentration of the polyamino acid for which the *in vivo* release time of the interferon(s) is prolonged beyond 24 h after administration.

This is not found persuasive because, based on the teachings in the art as a whole, one of skill in the art would have known how to determine the critical concentration.

10. Claims 1, 4, 5, 7-19, 22, 23, 28, 29, and 35 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-21 of U.S. Patent No. 7,919,572 (filed as Application No. 10/558,617). Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims and the application claims are drawn to the same polymer formulation for prolonged delivery of interferon, wherein the polymer is capable of forming a gel upon administration *in vivo* (i.e., in the presence of albumin). Since the polymer solution recited in the application claims is liquid before administration and forms a gel upon administration, it must have the polymer concentration and the viscosity recited in the instant claims. Thus, the instant claims and the patent claims are obvious variants.

The arguments are the same as the ones for Application No. 11/658,803. These arguments are not found persuasive for the reasons set forth above. Specifically, the patent claim 14, 15, and 17 recite a colloidal suspension or solution; the patent claim 18 recites that the polymer forms a gel at the injection site (i.e., after administration *in vivo*).

11. Claims 1, 4, 5, 7-19, 22, 23, 28, 29, and 35 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-18 of U.S. Patent No. 7,659,365, in view of each Regalado et al. (Macromolecules, 1999, 32: 8580-8588, of record), Dupuis et al. (U.S. Patent No. 6,607,714), and Bromberg et al. (U.S. Patent No. 5,939,485). Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims and the patent claims are drawn to the same polymer formulation for prolonged delivery of interferon. The patent claims do not recite gel-forming properties. However, modifying the patent claims to obtain injectable solutions capable of *in situ* gelling is suggested by the prior art. Controlled and prolonged drug release via injectable formulations capable of gelling *in vivo* was routine in the prior art. The prior art also suggests that the patent polymer is capable of forming a gel *in vivo* in the presence of physiological proteins. For example, the prior art teaches that incorporation of HG into hydrophilic polymers results in amphiphilic polymers which are capable of sol to gel transition depending on the amphiphilic polymer concentration (see Regalado et al., p. 8580, column 1; p. 8587, column 2). Dupuis et al. teach that amphiphilic polymer solutions are capable of forming gels in the presence of serum proteins such as albumin (Examples 4 and 5). Bromberg et al. teach the necessity of using responsive polymers capable of forming a gel in the presence of an environmental stimulus (such as a stimulus present *in vivo*), wherein adjusting the concentration of the responsive polymer gives the desired sol to gel transition (Abstract; column 2, lines 17, 18, and 63-65 ; column 6, lines 43-56; column 11, lines 20-40, claims 5, 18, and 32). Based on these teachings as a whole,

one of skill in would have known that the amphiphilic patent polymer is capable of sol to gel transition. One of skill in the art would also have reasonably expected that the polymer at concentrations promoting the sol to gel transition would be able to form a gel when injected *in vivo*, because albumin is present in blood and in the interstitial fluid. Therefore, one of skill in the art would have been motivated to vary the polymer concentration such as to determine the proper concentration needed to obtain a liquid formulation capable to form a gel in the presence of albumin (claim 3). It is noted that by doing such, one of skill in the art would have obtained a formulation capable of forming a gel deposit *in vivo* in the presence of physiological proteins.

Thus, the instant claims and the patent claims are obvious variants.

The arguments are the same as the ones for U.S. Patent No. 6,630,171. These arguments are not found persuasive for the reasons set forth above.

12. Claims 1, 4, 5, 7-19, 22, 23, 28, 29, and 35 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-24 of U.S. Patent No. 7,678,882. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims and the patent claims are drawn to the same polymer formulation for prolonged delivery of interferon, wherein the polymer formulation is capable of forming a gel upon administration *in vivo* (i.e., in the presence of albumin). Since the polymer solution recited in the patent claims is

liquid before administration and forms a gel upon administration, it must have the polymer concentration and the viscosity recited in the instant claims.

Thus, the instant claims and the patent claims are obvious variants.

The applicant argues that the U.S. Patent No. 7,678,882 does not disclose the existence of a relation between the critical concentration C 1 of the polyamino acid as determined by an IG test and the significant increase in the release time of interferon(s).

This is not found persuasive because, based on the teachings in the art as a whole, one of skill in the art would have known how to determine the critical concentration could. Furthermore, the IG test is not the only way to determine the critical concentration and thus, specifically using the IG test is not given patentable weight.

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. Claims 1, 4, 5, 7, 8, 12-16, 18, 22, 28, 29, 35-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Huille et al. (WO 00/30618), in view of each Regalado et al. (Macromolecules, 1999, 32: 8580-8588), Dupuis et al. (U.S. Patent No. 6,607,714), and Bromberg et al. (U.S. Patent No. 5,939,485).

The English language translation of WO 00/30618 is US Patent 6,630,171. The passages cited below which indicate the teachings of the '618 publication are based on its English translation (i.e., the '171 patent).

Huille et al. teach a liquid, low viscosity formulation suitable for parenteral injection and prolonged release of interferon, wherein the formulation is liquid in physiological medium and wherein the formulation comprises an aqueous colloidal suspension of submicronic particles in water and interferon(IFN) non-covalently-associated with the particles. The particles are made of homopolymers of α-aspartate or α-glutamate or of aspartate/glutamate copolymers (i.e., water-soluble polymers) carrying hydrophobic groups (HG), the HG could be cholesterol, the molar grafting rate is between 3 and 70%, the polymers contain up to 200 amino acids (i.e., n+m is 200) and the molecular weight of the polymer could be 20,000 g/mol; the polymers could have a structure as set forth in formula I (claims 1, 7, 16, 18, and 28) (Abstract; column 3, lines 25-65; column 4, lines 6-65; column 5, lines 45-61; column 9, lines 35-41; Example 1). Huille et al. also teach further attaching polyethylenimine (PEI) (claims 36 and 37) (column 7, lines 30-36).

Although Huille et al. teach homopolymers of α-aspartate or α-glutamate, they do not specifically teach that the amino acid precursors are L-aspartate or L-glutamate (claim 12-14). However, it would have been obvious to one of skill in the art to use such to achieve the predictable result of obtaining a polymer suitable for the controlled release of IFN. With respect to claim 15, Huille et al. teach their polymers as being either random or block polymers (column 7, lines 58-60).

Huille et al. do not specifically teach their HG being attached to the terminal ends of the polymer (i.e., formula IV recited in claim 8). However, it is noted that there is no evidence on the record that attaching the HG at the terminal ends of the polymer results in an unexpected property. The arrangement (i.e., where the HG is attached to the polymer) is not significant if it does not provide a novel feature. Moreover, it would have been obvious to one of skill in the art to vary the arrangement, with the purpose to achieve the optimum results. Absent evidence to the contrary, it is generally not inventive to discover the optimal arrangement of a prior art composition, such can be identified by routine experimentation.

Although Huille et al. teach a degree of association for insulin > 90% (Example 7), they do not specifically teach the same degree for IFN (claim 22). However, one of skill in the art would have reasonably expected to obtain the same high degree of association when using IFN.

Huille et al. do not specifically teach a polymer concentration which allows the formation of a gel deposit *in vivo* in the presence of at least one physiological protein (claims 1, 28, 29, and 35). However, controlled and prolonged drug release via injectable formulations capable of gelling *in vivo* was routine in the prior art. The prior art also suggests that the polymer of Huille et al. is capable of gel *in vivo* in the presence of physiological proteins. For example, the prior art teaches that incorporation of HG into hydrophilic polymers results in amphiphilic polymers which are capable of sol to gel transition depending on the amphiphilic polymer concentration (see Regalado et al., p. 8580, column 1; p. 8587, column 2). Dupuis et al. teach that amphiphilic polymer

solutions are capable of forming gels in the presence of serum proteins such as albumin (Examples 4 and 5). Bromberg et al. teach the necessity of using responsive polymers capable of forming a gel in the presence of an environmental stimulus (such as a stimulus present *in vivo*), wherein adjusting the concentration of the responsive polymer gives the desired sol to gel transition (Abstract; column 2, lines 17, 18, and 63-65 ; column 6, lines 43-56; column 11, lines 20-40, claims 5, 18, and 32). Based on these teachings as a whole, one of skill in would have known that the amphiphilic polymer of Huille et al. is capable of forming a sol to gel transition. One of skill in the art would also have reasonably expected that the polymer at concentrations promoting the sol to gel transition would be able to form a gel when injected *in vivo*, because albumin is present in blood and in the interstitial fluid. Therefore, one of skill in the art would have been motivated to vary the polymer concentration such as to determine the proper concentration needed to obtain a liquid formulation capable to form a gel in the presence of albumin (i.e., when injected *in vivo*). It is noted that by doing such, one of skill in the art would have obtained a formulation capable of forming a gel deposit *in vivo* in the presence of physiological proteins, wherein the formulation comprises a concentration of polymer as recited in claims 1 and 4 and wherein the viscosity is up to 5 Pas at 20ºC (claim 5).

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

The applicant argues that, although Huille teaches a liquid formulation suitable for parenteral injection and prolonged release of interferon, Huille does not specifically teach the existence of the relation between a critical concentration C 1 of the polyamino acid as determined by an IG test and the significant increase in the release time of interferon(s).

This is not found persuasive because the instant rejection is an obviousness-type rejection and thus, Huille does not have to teach each and every claimed limitation.

The applicant argues that the existence of a relation between the concentration C1 of the polyamino acid and an increase in the release time of interferon(s) was not obvious and one skilled person would not have found in Regalado how to determine the critical concentration C 1 of the polymer PO making it possible to prolong and control the in vivo release time of the interferon(s) beyond 24 h after administration.

This is not found persuasive because Regalado does not have to teach each and every claimed limitation. The existence of a correlation between the concentration of responsive polymers and gelling (i.e., controlled release) was common knowledge in the prior art (see the teachings of Bromberg et al. above). The IG test is not the only way to determine the critical concentration, one of skill in the art would have known how to accurately determine this concentration based on the teachings in the prior art. The applicant did not provide any evidence to the contrary. For the same reasons, the arguments related to Dupuis are not found persuasive.

The applicant argues that Bromberg teaches the necessity of using responsive polymers capable of forming a gel in the presence of an environmental stimulus. On the contrary, the current invention was designed to obtain a liquid pharmaceutical formulation that can delay the release of the interferon, without using temperature or pH change.

This argument is not found persuasive because it is directed to Bromberg individually. The rejection is based on a combination of references, which teaches that gels could be formed *in vivo* in the presence of stimuli other than pH and temperature. Specifically, Dupuis et al. teach that amphiphilic polymer solutions are capable of forming gels in the presence of serum proteins such as albumin. Bromberg teaches that gelling in the presence of environmental stimulus is correlated to the polymer concentration. Based on these teachings as a whole, one of skill in the art would have known that, when used at an appropriate concentration, Huille's polymers would form gels *in vivo* in contact with the albumin present in blood and tissues (i.e., in the presence of an environmental stimulus).

15. Claims 1, , 4, 5, 7, 8, 12-16, 18, 22, 23, 28, 29, and 35-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Huille et al. taken with Regalado et al., Dupuis et al., and Bromberg et al., in further view of Edwards et al. (Arch. Dermatol., 1990, 126: 1029-1032, Abstract).

The teachings of Huille et al., Regalado et al., Dupuis et al., and Bromberg et al. are applied as above for claims 1, 4, 5, 7, 8, 12-16, 18, 22, 28, 29, 35-37. Although

Huille et al., Regalado et al., Dupuis et al., and Bromberg et al. teach IFN, they do not specifically teach IFN-α (claim 23). Edwards et al. teach treatment of basal cell carcinoma via administration of controlled-release formulation comprising IFN-α (Abstract). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the formulation of Huille et al., Regalado et al., Dupuis et al., and Bromberg et al. by substituting their IFN with IFN-α to achieve the predictable result of obtaining a formulation suitable for the controlled-release of IFN-α.

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

The applicant argues that Edwards et al. do not cure the deficiencies noted above. This is not found persuasive because there is no deficiency to be cured.

16. Claims 1, 4, 5, 7, 8, 12-19, 22, 28, and 29, and 35-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Huille et al. taken with each Regalado et al., Dupuis et al., and Bromberg et al., in further view of both Kim et al. (U.S. Patent No. 5,869,703) and Seo et al. (U.S. Patent No. 7,311,901).

The teachings of Huille et al., Regalado et al., Dupuis et al., and Bromberg et al. are applied as above for claims 1, 4, 5, 7, 8, 12-16, 18, 22, 28, 29, 35-37. Huille et al., Regalado et al., Dupuis et al., and Bromberg et al. do not teach tocopherol (claim 17). However, using tocopherol to obtain biocompatible amphiphilic polymers is taught by the prior art (see Kim et al., column 1, lines 9-18, column 2, lines 20-55; Seo et al.,

Abstract, column 4, lines 10-30). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the polymer of Huille et al., Regalado et al., Dupuis et al., and Bromberg et al. by substituting their cholesterol with tocopherol to achieve the predictable result of obtaining a polymer suitable for prolonged IFN delivery. With respect to claim 19, it would have been obvious to one of skill in the art to vary the polymer concentration such as to determine the proper concentration needed to obtain a liquid formulation capable to form a gel *in vivo*.

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

The applicant argues that Kim et al. and Seo et al. do not cure the deficiencies noted above. This is not found persuasive because there is no deficiency to be cured.

17. Claims 1, 4, 5, 7-16, 18, 21, 28, 29, and 35-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Huille et al. taken with each Regalado et al., Dupuis et al., and Bromberg et al., in further view of Conover et al. (Anti-Cancer drug Design, 1999, 14: 499-506).

The teachings of Huille et al., Eliaz et al., Regalado et al., Dupuis et al., and Bromberg et al. are applied as above for claims 1, 4, 5, 7, 8, 12-16, 18, 22, 28, 29, 35-37. Huille et al., Regalado et al., Dupuis et al., and Bromberg et al. do not teach coupling their cholesterol via an amino acid spacer (claims 9-11). However amino acid spacers (including alanine and phenylalanine) were routinely used in the prior art to

create polymers suitable for drug delivery (see Conover et al., Abstract, p. 502, Tables I and II, p. 504, column 1). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the polymer of Huille et al., Regalado et al., Dupuis et al., and Bromberg et al. by using an amino acid spacer to couple the cholesterol to their polymer to achieve the predictable result of obtaining a polymer suitable for sustained release of TNF.

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

The applicant argues that Conover et al. do not cure the deficiencies noted above. This is not found persuasive because there is no deficiency to be cured.

Conclusion

18. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ILEANA POPA whose telephone number is (571)272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Ileana Popa/
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